ORIGINAL ARTICLE

Electron Beam Computed Tomography Evidence of Aortic Calcification as an Independent Determinant of Coronary Artery Calcification

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Background: Imaging of the aorta has received less attention than imaging of the coronary beds, despite the possible link between aortic and coronary artery disease (CAD). Electron beam computed tomography (EBCT) with 100 ms scanning speed can eliminate pulsation-related motion artifacts. The goals of this study were to evaluate EBCT-detected subclinical atherosclerosis over the whole aorta as in routine abdominal and thoracic CT scans and analyze whether or not the measurements of aortic calcification (AC) can independently predict the presence of coronary artery calcification (CAC), which is a surrogate marker of CAD.

Methods: A consecutive series of 196 adults (male:female, 127:69; mean age, 65.9 ± 10.5 years) were enrolled for EBCT examinations of the coronary arteries and whole aorta. CAC and AC were calculated by the Agatston method. Major cardiovascular risk factors were also recorded.

Results: The greatest amount of AC was seen at the abdominal aorta, followed by the descending aortic arch, thoracic aorta, and ascending aorta. Total AC was significantly correlated with CAC ($r = 0.51$, $p < 0.001$). After adjustment for major cardiovascular risk factors of age, gender, diabetes, hypertension, hypercholesterolemia, and family history, the three independent significant determinants of CAC were abdominal AC, thoracic descending AC, and male gender (model $r^2 = 0.495$, $p < 0.001$). For receiver operating characteristic analysis in predicting the presence of CAC, the threshold of descending AC was 11, with 68.3% sensitivity and 75.0% specificity. The optimal threshold of abdominal AC was 123, with 74.1% sensitivity and 67.9% specificity.

Conclusion: AC values in different portions of the aorta are independent predictors for the presence of CAC. [*J Chin Med Assoc* 2006;69(9):409–414]

Key Words: aorta, calcification, coronary artery, electron beam computed tomography

Introduction

In response to different humoral and hemodynamic insults, the systemic vasculature can undergo reparative mechanisms causing calcium deposition quite similar to that involved in the process of bone formation.[1,2] These calcium burdens are considered to be markers of subclinical vascular injury. Several large-scale epidemiologic surveys have demonstrated that calcium depositions in the abdominal aorta,[3,4] aortic arch,[5,6] and coronary arteries[7] can predispose people to increased cardiovascular morbidity and mortality.

Advances in electron beam computed tomography (EBCT) facilitate the sensitive and quantitative detection of vascular calcium deposits. By using EBCT with a scanning time of 100 ms, which is even faster than the most updated multidetector CT, we have applied coronary artery calcification (CAC) scores to evaluate angiographic coronary artery disease (CAD),[8] assess angiographically significant stenosis on an

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artery-by-artery basis,[9] and also differentiate patients with syndrome X from those with CAD.[10] In addition to the strong association with coronary events, CAC detected by EBCT is also closely related to pulmonary embolism[11] and stroke.[12] Some investigators have proposed that the associations between CAC and clinical cardiovascular events might be even stronger than those of the traditional Framingham study-based risk factors.[13] Therefore, early identification and timely intervention of patients at risk might substantially alleviate the incidence of later cardiovascular events.

Contrary to the extensive study of EBCT in CAC, imaging of the aorta has received less attention, despite autopsy findings having already highlighted the significant positive associations between aortic calcification (AC) and calcified plaque in the coronary arteries.[14] By using plain abdominal radiographs, the Rotterdam Coronary Calcification Study[15] demonstrated the association between CAC and abdominal AC. However, the limited resolution of plain X-rays may render inconsistent and relatively low sensitivity detection for AC.[16] Even with more sensitive CT techniques, most investigators have focused on thoracic AC to explore the association of AC with CAD.[17–19] To date, only a few comprehensive studies have applied EBCT in evaluating AC of the whole aorta.[20] The goal of the present work was to create a map of AC at different portions of the aorta and to evaluate its relationship with CAC.

Methods

Study population

A total of 196 consecutive patients who underwent EBCT at our radiology department to detect CAD were enrolled. Informed consent was obtained from all participants, and the study was approved by the institutional review board before implementation. Detailed health history questionnaires and chart records were obtained to evaluate all subjects' cardiovascular risk factors before undergoing the scanning procedure. Risk factors were dichotomized to absence *vs.* presence. Hypertension was defined by the current use of antihypertensive medications or systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg. Hyperlipidemia and diabetes mellitus (DM) were identified by self-report and concurrent use of lipid lowering or glycemic control medications, respectively. Smoking and family history of cardiovascular disease were assessed by questioning the patients. Smoking at any time before EBCT screening was considered to be a positive smoking status.

EBCT study

Coronary artery EBCT examinations were performed with the Imatron C-150 XP electron beam CT scanner (GE-Imatron, South San Francisco, CA, USA) in the single-slice, high-resolution volume mode. Under electrocardiogram gating, 30–40 consecutive images were obtained in diastole (80% R–R interval) at 3 mm section thickness.

Aortic images were obtained concordant with our routine thoracic and abdominal CT scanning protocol. Briefly, scans were performed with a 400 ms exposure time in the single-slice, high-resolution volume mode with a 30 cm field of view and a matrix size of 512 × 512. Approximately 70 tomographic images of 6 mm consecutive scans were obtained to cover the range from the aortic arch to the bifurcation in 2 breath-holding periods.

CAC and AC were calculated at the workstation by the Agatston method. Lesions were manually planimetered by an experienced technologist and reviewed by 2 radiologists. Threshold for defining a calcific lesion was set at a CT density >130 Hounsfield units, with an area >1.02 mm^2. CAC was measured for the 4 main coronary arteries and then summed to generate a total score. A lesion score was calculated by multiplying the density number by the area of the lesion in mm^2. Total calcium score was defined as the sum of lesion scores for all slices. AC was calculated in 4 divided locations of the aorta: ascending aorta, aortic arch, descending thoracic aorta (from pulmonary arteries to origin of celiac artery), and abdominal aorta (from celiac artery to iliac bifurcations). Calculated calcium scores were adjusted for slice thickness as follows: original score × slice thickness/3.0.

Statistical analysis

Statistics were analyzed using SPSS 11.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation for continuous variables and as proportions for categorical variables. Calcium scores were transformed as log(CAC + 1) or log(AC + 1) as previously reported[20] to reduce skewness and allow for multivariate analysis. Pearson's correlation coefficients were calculated to evaluate the relationship between CAC and AC in different portions of the aorta. Stepwise linear regression analysis was also performed to identify the independent determinants of log(CAC + 1). By calculating the ratios of individual partial r^2 to the full model r^2, the relative importance of each independent variable in the full model was determined. We used receiver operating characteristic (ROC) curves to find the optimal cutoff points of AC for classifying the presence/absence of CAC.

The best cutoff value was defined as the highest sum of sensitivity and specificity. A p value < 0.05 was considered statistically significant.

Results

A total of 196 consecutive patients were enrolled (mean age, 65.9 ± 10.5 years; 127 men, 69 women). Men were older (mean age, 67.8 *vs.* 62.8 years, $p < 0001$) and had a higher prevalence of smoking than women (22% *vs.* 3%, $p < 0.001$). Otherwise, there were no significant differences regarding prevalence of hypertension, hypercholesterolemia, DM, or family history of cardiovascular disease. The intra- and interobserver variabilities of CAC were 1.9% and 1.3%, respectively, and for AC were 0.6% and 0.5%, respectively.

Aortic calcification

Up to 89.2% (175/196) of our studied population had detectable AC. The prevalence and extent of calcification increased with age in each location of the aorta (Table 1). There were no significant gender differences regarding extent of AC in different locations of the aorta. For both genders and overall age groups, the abdominal aorta and aortic arch displayed the highest prevalence of calcium deposition, followed by the descending and ascending aortas. The extent of AC also tended to be most extensive over the abdominal aorta and aortic arch, followed by the descending and ascending aortas.

Coronary artery calcification

When scored by the Agatston system, 28.6% of patients (56/196) were normal (no CAC), whereas 41.8% (82/196) had mild calcification (CAC score, 1–10), 19.9% (39/196) had moderate calcification (CAC score, 11–100), and 9.7% (19/196) had severe calcification (CAC score ≥ 400). Calcium was present in the left main artery in 30.6% (60/196) of patients and in the left anterior descending, circumflex arteries, and right coronary artery in 57.7% (113/196), 32.7% (64/196), and 46.4% (91/196), respectively. A total of 20.9% (41/196) of patients had calcium in 1 coronary artery, 15.3% (30/196) in 2, 22.4% (44/196) in 3, and 11.7% (23/196) in all 4 major coronary arteries. Contrary to the trend in AC, men exhibited an increased prevalence and extent of CAC compared with women across each age stratum (Table 1).

Correlations between aortic and CAC

Overall AC was significantly correlated with CAC scores ($r = 0.51$, $p < 0.001$). The correlation coefficients between specific AC in an individual location and CAC are shown in Table 2. There seem to be gender differences regarding the relationship between AC and CAC. For men, descending and abdominal ACs were more closely related to CAC ($r = 0.514$ and 0.452, respectively), whereas in women, ascending and abdominal ACs were more closely associated with CAC ($r = 0.537$ and 0.513, respectively).

Stepwise linear regression

The stepwise linear regression with clinical variables (age, gender, presence of hypertension, hypercholesterolemia, DM, smoking, or family history) and AC as candidate independent variables, and log(CAC + 1) as the dependent variable showed that abdominal AC, thoracic descending AC, and male gender remained the independent and significant determinants of log(CAC +1) (Table 3). Together, these three determinants

Table 1. Prevalence and median calcium scores per age stratum*

	n	Ascending	Arch	Descending	Abdominal	Coronary artery
Male						
< 50	6	0 [0]	17 [0]	17 [0]	32 [0]	50 [1]
50–60	23	4 [0]	61 [11]	22 [0]	70 [43]	69.6 [29]
60–70	29	10 [0]	79 [134]	55 [2]	72 [186]	72.4 [7]
70–80	57	19 [0]	93 [586]	81 [132]	86 [454]	84.2 [70]
> 80	12	33 [0]	92 [506]	83 [451]	92 [753]	91.7 [298]
Female						
< 50	6	0 [0]	17 [0]	17 [0]	17 [0]	40 [0]
50–60	18	0 [0]	61 [34]	50 [1]	72 [40]	50 [1]
60–70	27	18 [0]	85 [112]	63 [15]	78 [127]	51.9 [1]
70–80	18	39 [0]	89 [485]	89 [304]	94 [603]	77.8 [21]
> 80	0					

**Data presented as prevalence (%) [median calcium score].*

Table 2. Correlations among coronary artery and aortic calcifications

	CAC	Ascending	Arch	Descending	Abdominal
Male					
CAC	1	0.343	0.437	0.514	0.452
Ascending	0.343	1	0.338	0.288	0.313
Arch	0.437	0.348	1	0.645	0.489
Descending	0.514	0.288	0.645	1	0.522
Abdominal	0.452	0.313	0.489	0.522	1
Female					
CAC	1	0.537	0.462	0.432	0.513
Ascending	0.537	1	0.354	0.382	0.409
Arch	0.462	0.354	1	0.750	0.786
Descending	0.432	0.382	0.750	1	0.647
Abdominal	0.513	0.409	0.786	0.647	1

$p < 0.001$ for all correlations; CAC = coronary artery calcification.

Table 3. Stepwise linear regression of determinants of coronary artery calcification (CAC)

Dependent variable	Total r^2	Independent variable	Partial r^2	Standardized coefficient	p
CAC	0.495	Abdominal aorta	0.363	0.348	0.001
		Thoracic descending aorta	0.094	0.388	< 0.001
		Male gender	0.038	0.216	0.016

account for 49.5% of the total variance. Abdominal AC alone represented 73.3% of explained variance (partial $r^2 = 0.363$, $p < 0.001$), followed by thoracic descending AC and male gender (partial $r^2 = 0.094$, $p < 0.001$ and $r^2 = 0.038$, $p = 0.016$, respectively).

ROC analysis

To further delineate the capability of AC in predicting the presence of CAC, ROC analysis was performed. The areas under the curve for abdominal and thoracic descending ACs were 0.723 and 0.746, respectively, with $p < 0.001$ for both. The optimal abdominal AC threshold from this analysis was 123 (Figure 1), with 74.1% sensitivity, 67.9% specificity, 84.8% positive predictive value, and 44.4% negative predictive value. For thoracic descending AC (Figure 2), the optimal threshold was 11, with 68.3% sensitivity, 75.0% specificity, and 85.0% positive and 50.7% negative predictive values.

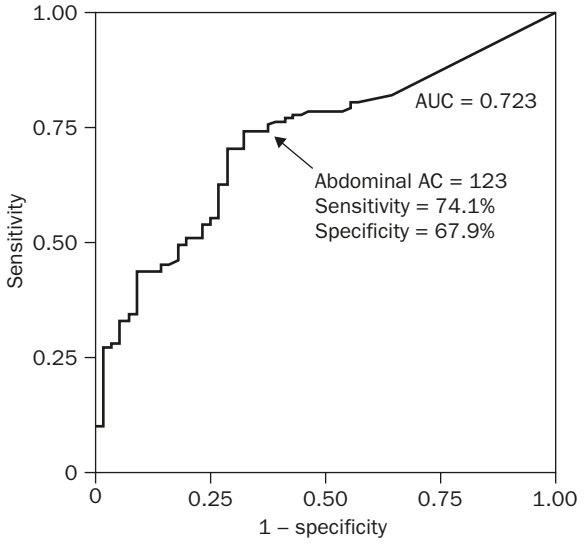

Figure 1. Receiver operating characteristic curve for abdominal aorta calcification (AC) and the presence of coronary artery calcification. AUC = area under the curve.

Discussion

In the current work, we comprehensively studied calcium distribution over the whole aorta and demonstrated that the presence of AC could predict CAC. Furthermore, AC in different portions could independently exert different effects on the extent of CAC, even in the presence of conventional cardiovascular risk factors.

To our knowledge, only one previous study applied EBCT to sketch the patterns of calcified atherosclerotic plaque across specific locations over

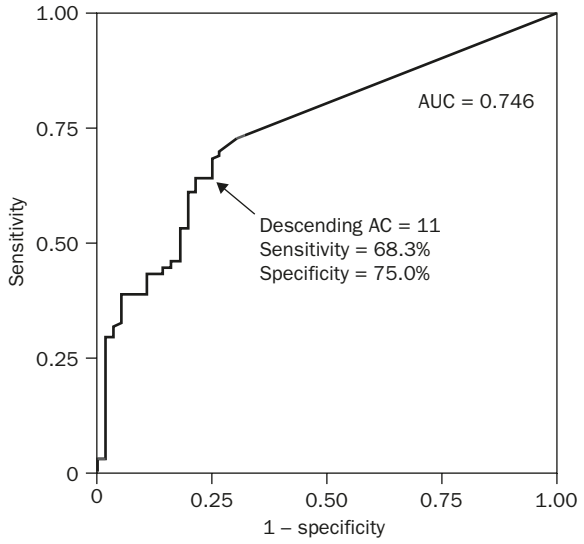

Figure 2. Receiver operating characteristic curve for descending aortic calcification (AC) and the presence of coronary artery calcification. AUC = area under the curve.

the length of the aorta with calcification in the coronary arteries.[19] Although both that study and ours used a 3 mm slice thickness for the coronary artery scans, we chose a 6 mm slice thickness to scan the whole aorta; Allison et al[19] adopted thickness of 5 mm for the thorax and 6 mm for the abdomen. Our study confirmed that the ascending aorta was the least commonly involved across all age strata, whereas the abdominal aorta exhibited the most extensive calcification. We speculate that different aortic geometries and various local tensile and shear stresses might contribute to different susceptibilities at different locations in the aorta for calcium deposition. We also demonstrated that males appear to have more extensive calcium deposition across both the aorta and coronary arteries. Concordantly, we found no gender differences regarding the prevalence of AC, whereas males displayed increased prevalence of CAC across all age strata. When compared with males in each corresponding age stratum, postmenopausal females tended to have strikingly increased atherosclerosis over the descending and abdominal aortas. These results support the possible protective effects of sex hormones associated with premenopause against the development of atherosclerosis.

The present EBCT studies further clarified that calcifications in the large-capacitance aorta can be associated with calcification in the conduit coronary arteries. When taking whole AC into consideration, our experience is similar to that of Raggi et al[20] regarding modest correlations between overall AC and CAC ($r=0.51$ *vs.* $r=0.48$). When considering correlations between specific AC and CAC, however, our experience was quite different from the only comparable report in the literature, by Allison et al,[19] who found similar correlation across specific AC and CAC for both genders. We observed that calcifications in the descending and abdominal aortas were more closely related to CAC in males, whereas calcifications in the ascending and abdominal aortas were more tightly associated with CAC in females. These gender predilections should be kept in mind by radiologists when interpreting AC.

Notably, abdominal AC in our series could independently explain up to 74.7% of the variance of CAC, even after adjustment for major cardiovascular risk factors. As proposed at the 34th Bethesda Conference, noninvasive atherosclerotic imaging could improve the detection of individuals at risk for ischemic heart disease.[21] Several EBCT studies have already provided evidence that analyzing AC and its respective significance with CAC could identify patients at risk for CAD or peripheral artery disease. In a series of 99 patients receiving both EBCT and coronary angiography, Yamamoto et al[17] found that the presence of calcification in the descending aorta could significantly increase the specificity of CAC to detect CAD (55% when CAC score > 0 *vs.* 88% when CAC > 0 plus descending AC > 0) and multiple vessel disease (41% when CAC score > 0 *vs.* 87% when CAC > 0 plus descending AC > 0). In 309 patients with type 2 diabetes who had inadequate glycemic control, Reaven and Sacks[22] further demonstrated that abdominal AC could have an independent and incremental benefit beyond that of traditional cardiovascular risk factors as a surrogate marker for diagnosis of clinical vascular disease. They proposed that the combination of CAC and AC scores could have an even closer association than either alone with peripheral artery disease. All these results convey the notion that atherosclerosis in different vascular beds could be an epiphenomenon of total atherosclerotic burden and reflect the likelihood of involvement of the remaining vascular beds.

It remains obscure as to what extent AC is clinically significant. Previously published reports mostly adopted semiquantitative scoring methods and mainly focused on portions of the thoracic aorta simultaneously obtained during coronary artery imaging. With the use of conventional helical CT, Watanabe et al[18] employed a dichotomized 2-point scale (absence or presence of calcification) to quantify calcification over 4 locations of the thoracic aorta (i.e. ascending aorta, inner curve of the aortic arch, aortic arch not including the inner curve, and thoracic descending aorta). They observed that increased AC in thoracic locations

combined with coronary risk factors was associated with higher likelihood of CAD. Because calcification of the abdominal and thoracic descending aortas was independently associated with CAC in our study, we performed ROC analysis to probe the optimal AC threshold for predicting the presence of CAC. By applying the 6 mm slice thickness routinely used for evaluating thoracic and abdominal organs, we observed that a calculated abdominal AC of 123 (sensitivity 74.1%, specificity 67.9%) and thoracic descending AC of 11 (sensitivity 68.3%, specificity 75.0%) could predict the presence of CAC. Therefore, our observations might be extrapolated to say that calculations of the aorta could provide additional diagnostic information for subclinical CAD. However, it should also be noted that our observations were based on a population with clinical suspicion of CAD that might have greater prevalence of CAC and CAD. Therefore, further large-scale studies in the general population are required to confirm our observations before they can be applied to daily practice. The present study was also limited by only discussing the effects of age and gender on AC and CAC, without taking other risk factors such as blood pressure and lipid profiles into consideration. Furthermore, other noninvasive techniques such as B-mode echography appear to be more powerful and cost-effective for the evaluation of extracoronary arteries, especially the abdominal aorta.

In conclusion, the association between AC and CAC reflects an underlying systemic vascular atherosclerotic process. Because AC is an independent determinant of CAC, the presence of calcium in the thoracic and/or abdominal aorta should prompt further cardiovascular assessments.

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